UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/762,602	03/21/2001	Petros Karouzakis	1581/128WO	6697

2101 7590 09/05/2003

BROMBERG & SUNSTEIN LLP
125 SUMMER STREET
BOSTON, MA 02110-1618

EXAMINER
HUI, SAN MING R

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 09/05/2003

22

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/762,602	KAROUZAKIS ET AL.	
	Examiner	Art Unit	
	San-ming Hui	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2003 and 8 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-31,33-42 and 48-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-31, 33-42, and 48-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's amendments filed May 28, 2003 and June 8, 2003 have been entered.

The cancellation of claims 32 and 43-47 in amendments filed May 28, 2003 is acknowledged.

The addition of claims 48-54 in amendments filed May 28, 2003 is acknowledged.

Claims 27-31, 33-42, and 48-54 are pending.

The outstanding rejections under 35 USC 112, first and second paragraph are withdrawn in view of the amendments filed May 28, 2003.

The outstanding rejection under 35 USC 102(b) is withdrawn in view of the amendments filed May 28, 2003.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 27-31, 33-42, and 50-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lowrey (US Patent 5,981,563), Neal (US Patent 6,103,765), Nahoum (US Patent 5,773,457) and Buyuktimkin et al. (US Patent 6,046,244) in view of El-Rashidy (US Patent 5,256,652), and Reilly (chapter 80 in Remington: The Science and

Practice of Pharmacy, page 1397, 1509-1512), references of record in the previous office action.

Lowrey teaches that the sexual response in females involve vasodilation and engorgement of the genitalia with arterial blood in a manner analogous to the male erectile response (See col. 5, line 38-51). Lowery further teaches that vasodilators facilitate increase blood flow to the genitalia is useful as modulating female sexual response (See col. 17, line 22-52).

Neal teaches misoprostol and alprostadil are known and preferred vasodilating agents for treating male sexual dysfunction (See col. 3, line 48-52).

Nahoum teaches that both misoprostol (a prostaglandin E_1 analog) and alprostadil (a prostaglandin E_1), among other vasoactive agents, are useful in treating female sexual dysfunction (See col. 9, lines 47-48; lines 53- col.10, line 1). Nahoum also teaches that the female sexual dysfunction treating composition, which may contain misoprostol, can be administered topically as gel, cream or ointment (See particularly col. 10, line 48-49). Nahoum also teaches that penetration enhancing agent may be incorporate into the female sexual dysfunction treating composition, which may contain misoprostol (See col. 14, line 8 - col. 15, line 48).

Buyuktimkin et al. teaches that a topical prostaglandin E_1 (PGE_1 also known as alprostadil) composition, which has penetration enhancer composition in it, is useful for treating any disease that is treated by prostaglandin E_1 (see col.1, line 27-28 and col. 8, line 6-8). Buyuktimkin et al. also teaches the amount of the active prostaglandin ingredient to be 0.1-0.5 %w/v (See col. 10, Table 1).

The primary references do not expressly teach that the topical sexual dsyfunction treating composition employs misoprostol or misoprostol and alprostadil in combination particularly. The primary references do not expressly teach that the amount of misoprostol to be 0.3-0.9%. The primary references do not expressly teach the application of the topical prostaglandin composition in a method of treating female sexual dysfuntion to the vagina or clitoris. The primary references do not expressly teach the female sexual dsyfunction treating method comprising α-cyclodextrin, gelatin, and hydroxymethylcellulose. The primary references do not expressly teach the female sexual dsyfunction treating method comprising hydroxypropyl methylcellulose which comprises hydroxypropyl methylcellulose 3000 in the amount of 4% w/v.

El-Rashidy teaches a topical sexual dysfunction treating composition that comprises a vasodilating agent, α-cyclodextrin, and hydroxypropyl methylcellulose (See col. 3, line 67-68; col. 6, line 2-4). El-Rashidy also teaches that the amount of hydroxypropyl methylcellulose is 2-3%w/v (See col.8, Table II).

Reilly teaches that gelatin is useful as an emulsifying agent utilized to formulate topical formulation (page 1397, col. 1; also page 1510 col.1, last paragraph).

It would have been obvious for one of ordinary skill in the art at the time the invention was made to apply a topical female sexual dysfunction treating composition of misoprostol in the amount of 0.3-0.9% with or without the second vasoactive agent onto the vagina or clitoris. It would have been obvious for one of ordinary skill in the art at the time the invention was made to incorporate α-cyclodextrin, gelatin, and hydroxyproopyl methylcellulose, which comprises hydroxypropyl methylcellulose 3000 in the amount of

4%, into the topical female sexual dysfunction treating composition in a method to treat female sexual dysfunction.

One of ordinary skill in the art would have been motivated to apply the sexual dsyfunction treating composition, employing misoprostol in the amount of 0.3-0.9%, with or without another vasodilator, cyclodextrin, gelatin, and hydroxypropyl methylcellulose, which comprises hydroxypropyl methylcellulose 3000 in the amount of 4%, onto the vagina or clitoris in a method to treat female sexual dysfunction. Vasoactive agents are known to be useful to modulate female sexual response and treat female sexual dysfunction thereby, very much in the same way as male sexual dysfunction. Furthermore, misoprostol and prostaglandin E_1(alprostadil) are known to be vasodilating agents and have been used as preferred vasoactive agents for male sexual dysfunction. Therefore, employing known vasodilating agents, such as misoprostol and alprostadil specifically, in the treatment of female sexual dysfunctions would be reasonably expected to be effective, absent evidence to the contrary. In addition, topical formulation of alprostadil is known, substituting or incorporating misoprostol into such topical formulation of Buyuktimkin et al. would be reasonably expected to be effective in treating female sexual dysfunction.

Moreover, it is known in the art that increasing female sexual response is associated with vasodilation and engorgement of the genitalia with arterial blood. Therefore applying a composition containing known vasodilating agents, including the instant compounds directly onto any area of the genital would have been reasonably

expected to be effective in causing vasodilatation and engorgement of the genitalia; and thereby treating female sexual dysfunction.

In addition, incorporating known topical pharmaceutical composition excipients such as cyclodextrin, gelatin, and hydroxypropyl methylcellulose such as hydroxypropyl methylcellulose 3000 (hydroxypropyl methylcellulose with a specific molecular weight) that are well known to be useful additives in forming topical compositions is considered within the skill of artisan.

Furthermroe, optimization of result effect parameters (e.g., the amount of ingredients such as hydroxymethylcellulose and misopriostol) is obvious as being within the skill of the artisan, absent evidence to the contrary.

Claims 48-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nahoum (US Patent 5, 773,457).

Nahoum teaches that both misoprostol and alprostadil are useful in treating female sexual dysfunction (See col. 9, lines 47-48; lines 53- col.10, line 1). Nahoum also teaches that misoprostol and alprostadil may be formulated into topical composition and that the topical female sexual dysfunction treatment composition may contain carboxy methylcellulose which is a known to be useful as gel-forming agent (See particularly col. 13, line 46-48).

It would have been obvious for one of ordinary skill in the art at the time the invention was made to incorporate carboxymethyl cellulose and a second vasodilating

agent such as alprostadil into the misoprostol-containing female sexual dysfunction treating composition of Nahoum.

One of ordinary skill in the art would have been motivated to incorporate carboxymethyl cellulose into the misoprostol-containing female sexual dysfunction treating composition of Nahoum because carboxy methylcellulose is a known to be useful as gel-forming agent and incorporating such well-known gel-forming agent into the ocmpositoin of Nahoum in forming a gel composition is obvious as being within the purview of the skilled artisan, absent evidence to the contrary.

The motivation of incorporating a second vasodilating agent such as alprostadil, into the misoprostol-containing female sexual treating composition of Nahoum is provided by the cited prior art since combining two or more agents which are known to be useful as vasodilating agent individually into a single composition useful for the very same purpose is prima facie obvious. See *In re Kerkhoven* 205 USPQ 1069. Absent evidence to the contrary, no such evidence was seen to be present herein.

It is applicant's burden to demonstrate unexpected results over the prior art. See MPEP 716.02, also 716.02 (a) - (g). Furthermore, the unexpected results should be demonstrated with evidence that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance. *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992). Moreover, evidence as to any unexpected benefits must be "clear and convincing" *In re Lohr*, 137 USPQ 548 (CCPA 1963), and be of a scope reasonably commensurate with the scope of the subject matter claimed, *In re Linder*, 173 USPQ 356 (CCPA 1972). In the instant case, there is no examples or

clinical studies presented for the evaluation of unexpected effectiveness of the instant invention. Therefore, no convincing and clear unexpected result over the cited prior art is seen.

Response to Arguments

Applicant's arguments filed May 28, 2003 averring the cited prior art's failure to teach the claimed invention have been fully considered but they are not persuasive. From the teachings of the primary references, i.e., Lowrey, Neal, and Nahoum, one of ordinary skill in the art would see the following: 1) the herein claimed agents, misoprostol and alprostadil, are vasodilating agents; 2) female sexual response involves vasodilatation process; 3) misoprostol and alprostadil are known to be used in female sexual dysfunction treatment; 4) misoprostol and alprostadil are known to be administered topically. Taking with the teachings of the secondary references, which teach the commonly known excipients for topical composition, one of ordinary skill in the art would be motivated to employ the misoprostol and alprostadil containing composition to treat female sexual dysfunction topically.

Applicant's arguments filed May 28, 2003 averring the cited prior art's failure to suggest the administration of the herein claimed compounds to the vagina or clitoris for treating sexual dysfunction have been considered but are not found persuasive. The cited prior art clearly teaches the sexual response in females involve vasodilation and engorgement of the genitalia with arterial blood in a manner analogous to the male erectile response (See Lowrey, col. 5, line 38-51). Lowrey further teaches that

vasodilators facilitate increase blood flow to the genitalia is useful as modulating female sexual response (See col. 17, line 22-52). Since it is clear that vasodilation in the female genitalia is involved in female sexual response, employing a vaodilating agent o the female genitalia, such as vagina and clitoris, would be reasonably expected to be effective in female sexual dysfunction treatment, absent evidence to the contrary.

Applicant's arguments filed May 28, 2003 averring the Nahoum's filure to teach or suggest the route of administration have been considered, but are not found persuasive. Nahoum clearly teaches the female sexual dysfunction treating composition, which may contain misoprostol, can be administered topically as gel, cream or ointment (See particularly col. 10, line 48-49). Nahoum also teaches that penetration enhancing agent may be incorporate into the female sexual dysfunction treating composition, which may contain misoprostol (See col. 14, line 8 - col. 15, line 48). Therefore, possessing the teachings of Nahoum with that of other cited references, as a whole, one of ordinary skill in the art would have been reasonably expected to employ the herein claimed compounds to treat female sexual dysfunction topically, absent evidence to the contrary.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a

reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). As discussed above, possessing the teachings of the cited prior art, one of ordinary skill in the art would have been reasonably expected to employ the herein claimed compounds to treat female sexual dysfunction topically, absent evidence to the contrary.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (703) 305-1877. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

San-ming Hui
Patent Examiner

SREENI PADMANABHAN
PRIMARY EXAMINER 9/3/03